REMARKS

Claims 1 – 30 are in this Application.

Claims 2, 18 and 19 have been previously withdrawn. Claims 12 and 25 have been previously canceled.

Claims 1, 3-11, 13 -17 and 20 -30 are pending.

The Examiner has rejected claims 1, 3-17 and 20 -24 and 26 -30 under 35 U.S.C. §§ 103(a), and 112, second paragraph and further objects to claim 28.

Claims 1, 3, 9, 17, 21 – 23 and 28 and have been amended herein to more clearly define Applicant's invention. Support can be found throughout the claims, specification and abstract, specifically support can be found in the claims themselves and in the specification beginning on page 18, line 3 through to page 25, line 36.

No new matter has been added.

Claim Objections

The Examiner objects to claim 28. Claim 28 is objected to as being dependent on claims 18 – 19 which contain non-elected inventions. Applicant thanks the Examiner for pointing out this oversight. Claim 28 has amended so that it only depends on elected material. Specifically Claim 28 as amended only depends on elected Claim 17. In view of the foregoing applicant submits that the form of the claims is now in order and respectfully requests that the Examiner withdraw the objections to Claim 28.

Claim Rejections – 35 U.S.C. § 112, second paragraph

The Examiner has rejected claims 1, 3-11, 13 - 17, and 20 – 24 and 26 – 30 under 35 U.S.C. §112 , second paragraph maintaining that the claims are not definite.

Applicant has amended Claims 1 and 17 change the phrase "RR3 is a third recombination element ..." to "RR3 is a third recombination region ..." Support for this claim can be found throughout the specification, claims and abstract, and specifically in the specification on page 18, lines 15 – 26. This amendment provides antecedent support for "recombination region" specified in step c)(ii) of claims 1 and 17.

Applicant has amended Claim 3 to remove the reference to a second expressible DNA fragment for which there is insufficient antecedent basis.

Applicant has amended claims 9, and 23 to change the term "regulatory region" which has insufficient antecedent basis to "regulatory circuit" which has antecedent support in Claim 1 and 17.

The May 25, 2006 Office Action states Claim 20 is vague and indefinite because it recite the phrase "said promoter" which the might be ambiguous. Although, Claim 20 reads:

> A method according to Claim 17 wherein the site-specific recombinase is expressed by a gene residing on a plasmid.

The phrase "said promoter" does not appear in Claim 20 as recited. However, the Applicant has amended claims 21 and 22 to specifically recite "said foreign promoter" to clarify which promoter Applicant is referring to in these claims.

Claim 17 has been amended to clarify that the *E. coli* is the host cell.

Claims 1, 3, 9, 17, and 20 – 22 as amended here particularly point out and distinctly claim subject matter of the instant invention. Further Claims 4 – 8, 10, 11, 13 – 16, 20 – 22, 24 and 36 – 30 depend on claims that particularly point out and distinctly claim subject matter of the instant invention.

Claim Rejections – 35 U.S.C. § 103(a)

The May 25, 2006 Office Action rejects Claims 1, 3 – 11, 13 –17, 20 – 24 and 26 – 30 Under 35 U.S.C. 103(a) as being anticipated by Perkins et al. (Application Publication No. 2002/0151058) ('Perkins' hereafter) in view of Yu et al. (PNAS (2000) 97:5978- 5983) ('Yu' hereafter) in further view of Prideaux et al. (U.S. Patent No. 6,472,183) ('Prideaux' hereafter). Applicants traverse. The Office Action dated December 20, 2005 states on page 9, that Perkins is the closest prior art, and further records, "Perkins and Tugendreich do not teach the use of the λRed recombination system, recombination into the bacterial chromosome or a second recombination reaction to eliminate the selectable marker." The present 103(a) rejection is an amalgamation of Perkins and two other references selected to provide the parts of the invention that Perkins did not teach as specified by the December 20 Office Action. The three individual elements may have existed individually before the date of filing, however, similar to the present invention that is a combination of three known types of nucleic acid molecules into a succinct and elegant system, the invention itself is a non-obvious and novel combination of three elements of art into a new invention. Even if Perkins, Yu and Prideaux contain all the elements of the present invention (although the Applicant protests that they do), one of ordinary skill in the art would not have the motivation to combine Perkins, Yu and Prideaux to create the present invention.

The May 28, 2006 Office Action on page 6 suggests that one skilled in the art would be motivated to combine Perkins and Yu "because, Yu et al teach that it is difficult to recombine linear DNA into *E. coli* genomes and that this system is an improvement over the art at the time when the invention was made." However, the triple recombination system of Perkins in Fig. 3 as cited in the Office Action is not linear DNA, but rather a circular vector. Such vectors are well know to be used to stably transform bacteria especially *E. coli* bacteria. The problem cited by Yu, that is the normal exonuclease activity that degrades linear DNA is not a problem for the artisan practicing Perkins with a circular plasmid vector. Therefore one skilled in the art practicing Perkins would not have the problem suggested by Yu nor would the artisan recognize Yu as a potential part of a new method because Yu discusses linear fragment and Perkins is directed to circular stable vectors.

The May 28 Office Action on page 8 suggest that, "it would have been obvious to one of ordinary skill in the art to modify the methods of Perkins et al to include a selectable marker flanked by recombination sequences so that the selectable marker could be excised from the host chromosomes after homologous recombination because Perkins et al teach a method of introducing DNA sequences into bacterial genome for production of genes of interst using selectable markers to screen for the presence of the introduced vector and Prideaux et al teach that genes for antibiotic resistance used for the selection can be undesirable after selection has taken place." However, this reasoning is flawed when the selectable marker is considered in the context of the Perkins system. Perkins taken alone teaches the uses of a plasmid vector with a select marker. The selectable marker has a two fold function, first it is used to identify transfected bacteria that contain the gene of interest for isolation. Second it is used to maintain the plasmid in the isolated bacteria population for the production of the gene of interest. It is well known to one of ordinary skill that a plasmid can be lost if the growth of the bacteria culture is not continually selected for a trait contained within the plasmid. Therefore, one skilled in the art practicing Perkins would not be motivated to combine with Prideaux to introduce flanking recombination sequences because the skilled artisan would desire to retain the selectable marker to properly practice Perkins. The selectable marker is crucial to the practice of Perkins as disclosed and therefore one skilled in the would want to increase the selection for the marker and not be motivated to eliminate said marker as described in Prideaux.

One skilled in the art practicing Perkins with a stable transfected gene of interest on a circular plasmid would not be motivated to adopt a system for chromosomal integration designed for linear fragments. Said skilled artisan does not have a need for chromosomal integration. Without first incorporating the gene of interest into the chromosome, combining Prideaux and Perkins together would be a fatal combination. Using a second recombinase reaction to eliminate the selectable marker as suggested by Prideaux destroys the stably of the vector as transfected by the Perkins system. It would take an inventive step such as described in the instant application to use a triple homologous recombination event, combined with the λRed system for bacterial chromosome integration, and incorporating a flanking recombination sequence so that after chromosomal integration has been achieve and stably ensured the selectable marker can be removed.

One skilled in the art practicing Perkins would not be motivated to construct the removable of a necessary component of the Perkins system, that is the selectable marker, by a second recombinase reaction. Also one of ordinary skill would not be motivation by Yu to combine chromosome incorporation into the already stable and effective practice of Perkins, especially considering that Yu is directed to the problems of a linear fragment and the artisan has a circular stable plasmid that is not subject to the problem that Yu solves. Applicant

respectfully requests the Examiner remove of all rejections under 35 U.S.C. § 103(a) in view of Perkins, Yu and Prideaux.

The May 25, 2006 Office Action rejects Claims 1, 3 – 11, 13 –17, 20 – 24 and 26 – 30 Under 35 U.S.C. 103(a) as being anticipated by Perkins et al. (Application Publication No. 2002/0151058) in view of Yu et al. (PNAS (2000) 97:5978- 5983) in further view of Welch et al. (Application Publication No. 2002/0187544) ('Welch' hereafter) as evidenced by Guzman, et al. (J Bacteriol. 1995, 177(14): 4121-4130) ('Guzman' hereafter). This 103(a) rejection like the above rejection also does not provide sufficient motivation to combine the references. Even if Perkins, Yu, Welch and Guzman contain all the elements of the present invention (although the Applicant protests that they do), there is not sufficient motivation to combine. As discussed above Yu is directed to the stablity problem of linear DNA fragments, whereas Perkins utilizes a circular vector that is not degraded by exonuclease activity.

The May 28, 2006 Office Action stated on page 13 that it would have been obvious to one practicing Perkins to incorporate Welch's "excisable selectable marker system because Perkins et al teaches the methods of introducing promoters and genes of interest into a bacterial chromosome". However this contradicts the statement on page 9 of the December 20, 2006 Office Action, "Perkins and Tugendreich do not teach ... recombination into the bacterial chromosome..." (full quote above). The fact is that Perkins do not teach nor require bacterial chromosome integration. Perkins convey stability of transfection by use of a selectable marker on a circular plasmid. The skilled artisan would be aware of the importance of the selectable marker to the stably of the plasmid in the bacteria population and would take step to maintain said marker not to eliminate it. Perkins effectively teach away from excising the selectable marker. There is no motivation to combine Perkins with Welch or Guzman, neither is motivation to combine Perkins with Yu. Applicant respectfully requests the Examiner remove of all rejections under 35 U.S.C. § 103(a) in view of Perkins, Yu, Welch and Guzman.

CONCLUSION

In view of the foregoing Amendments and Remarks, Applicant respectfully requests reconsideration of the claims and removal of all objections and rejections. Therefore, the Applicant submits that Claims 1, 3 – 11, 13 –17, 20 – 24 and 26 – 30 are in condition for allowance and it is respectfully requested that a patent be issued on these claims.

Respectfully submitted,

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